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MESSAGE:

Applicants: Jennifer L. West and Brenda K. Manning

Serial No.: 09/935,168 Art Unit: 1644

Filed: August 21, 2001 Examiner: Phuong N. Huynh

For: *TISSUE ENGINEERING SCAFFOLDS PROMOTING MATRIX PROTEIN PRODUCTION*

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PTO/SB/21 (08-03)
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	09/935,168
Filing Date	August 21, 2001
First Named Inventor	Jennifer L. West et al.
Art Unit	1644
Examiner Name	Phuong N. Huynh
Total Number of Pages in This Submission: 29	Attorney Docket Number: RICE 103

ENCLOSURES *(Check all that apply)*

- [x] Fee Transmittal Form
- [ ] Fee Attached
- [ ] Amendment/Reply
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Petition for Reconsideration of Restriction Requirement

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Signature	Rivka D. Monheit
Date	February 3, 2004

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Effective 10/01/2003. Patent fees are subject to annual revision.

☑ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 165.00

Complete if Known	
Application Number	09/935,168
Filing Date	August 21, 2001
First Named Inventor	Jennifer L. West et al.
Examiner Name	Phuong N. Huynh
Art Unit	1644
Attorney Docket No.	RICE 103

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($) 0.00

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

	Extra Claims		Fee from below	Fee Paid
Total Claims	9 - 20** =		X	= 0.00
Independent Claims	1 - 3** =		X	= 0.00
Multiple Dependent				

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

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FEE CALCULATION (continued)

3. ADDITIONAL FEES

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1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	165.00
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

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SUBTOTAL (3) ($) 165.00

SUBMITTED BY

(Complete *if applicable*)

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Signature	Rivka D. Monheit			Date	February 3, 2004

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: Jennifer L. West and Brenda K. Manning

Serial No.: 09/935,168 Art Unit: 1644

Filed: August 21, 2001 Examiner: Phuong N. Huynh

For: *TISSUE ENGINEERING SCAFFOLDS PROMOTING MATRIX PROTEIN PRODUCTION*

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Alexandria, VA 22313-1450

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 1-9 in the Office Action mailed September 2, 2003, in the above-identified patent application. A Notice of Appeal was mailed on December 3, 2003. The Commissioner is hereby authorized to charge $165.00, the fee for filing this Appeal Brief for a small entity, to Deposit Account No. 50-1868. It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-1868.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is the assignee, Rice University, Houston, Texas.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to Appellants, the undersigned, or Appellants' assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS ON APPEAL

Claims 1-9 are pending and on appeal. The Examiner has withdrawn claims 3-5 as being directed to a non-elected invention. However, Appellants have petitioned to have claims 3-5 rejoined in the application due to improper restriction requirement. Therefore, these claims will also be argued as being patentable.

(4) STATUS OF AMENDMENTS

An appendix sets forth the claims on appeal.

(5) SUMMARY OF THE INVENTION

The claims are directed to a method for making a tissue engineering scaffold for inducing formation of extracellular matrix by cells attached to the scaffold (page 3, lines 5-9) by coupling matrix-enhancing molecules to the scaffold (page 7, lines 6-8) in an effective density to elicit production of extracellular matrix without increasing cellular proliferation (page 1, lines 4-7; page 4, line 29 – page 5, line 2; page 7, lines 12-13). When the matrix-enhancing molecules are TGF-β (page 2, line 30 – page 3, line 1), the TGF-β is coupled to the matrix by a polymer tether having a molecular weight between 2000 and 6000 (page 7, lines 3-5) and is in a density between 1 to 100 ng TGF-β/mL (page 7, lines 16-19) or in a concentration of between about 4×10^{-6} and 4×10^{-3} nmol/mL (page 7, lines 19-20). In addition to TGF-β, the matrix-enhancing molecules

may be angiotensin II, insulin-like growth factor and ascorbic acid (page 6, lines 10-11). In one embodiment, the matrix-enhancing molecules are covalently coupled to tethers which are covalently coupled to the scaffold (page 7, lines 6-10). Cells may also be attached to the scaffold (page 5, lines 23-24; page 6, lines 3-5).

The tissue engineering scaffold may be a hydrogel (page 5, line 14), for example, a hydrogel formed of a polymer such as alginate, collagen, hyaluronic acid, and polyethylene glycol polymers (page 5, lines 8-18). Matrix-enhancing molecule TGF-b may be coupled to the hydrogel in a concentration of between about 4×10^{-6} and 4×10^{-3} nmol/mL (page 7, lines 19-20).

(6) ISSUES ON APPEAL

The issues presented on appeal are:

(1) whether claims 1-2 and 6-9 were properly rejected under 35 U.S.C. § 103(a) as obvious over WO 94/23740 to Celtrix Pharmaceuticals, Inc. in view of Dinbergs et al., *J. Biol. Chem.* 271(47): 29822-29829; 1996 ("Dinbergs").

(2) whether claims 1-2 and 6-9 were properly rejected under 35 U.S.C. § 103(a) as obvious over WO 96/27657 to Massachusetts Institute of Technology in view of Dinbergs.

(7) GROUPING OF CLAIMS

The claims do not stand or fall together. The claims can be grouped as follows: (1) claim 1; (2) claim 2; (3) claims 3 and 5; (4) claim 4; (5) claim 6; and (6) claims 7-9. Reasons for this grouping and arguments for the separate patentability of these groups of claims are provided below.

(8) ARGUMENTS

(a) The Claimed Invention

Biomaterials developed for tissue engineering and wound healing applications need to support adequate cell adhesion while being replaced by new tissue synthesized by those cells. In order to maintain proper mechanical integrity of the tissue, the cells must generate sufficient extracellular matrix. Decreased extracellular matrix production by cells in tissue engineering scaffolds may lead to reduced structural integrity of the developing tissue. The proteins in the extracellular matrix largely determine the mechanical properties of the tissue resulting from the scaffold and are often needed to replace the functions of the scaffold material. While there are a number of references that disclose attaching growth factors such as TGF-β to polymeric scaffolds, none of the references describe how one can achieve enhanced production of extracellular matrix, ***while not increasing cellular proliferation***. In many tissue engineering applications it is important to avoid an undesirable increase in cellular proliferation. For example, in vascular tissue engineering, over-proliferation of the smooth muscle cells can lead to failure of the tissue engineering construct due to lumenal narrowing. Increased cellular proliferation can also lead to inflammation and scarring.

The claimed invention is not directed to increasing or decreasing cellular proliferation, but rather, to controlling (i.e., increasing) production of extracellular matrix to strengthen the tissue engineering scaffold independent of cellular proliferation. Appellants have devised a method of making a tissue engineering scaffold for inducing formation of extracellular matrix by cells bound to the scaffold by coupling matrix-enhancing molecules to the scaffold in an

effective density to elicit production of extracellular matrix without increasing cellular proliferation. Enhanced extracellular matrix production is believed to be due to an increase in gene expression, not a change in cell proliferation.

(b) Rejections under 35 U.S.C. § 103

i. The legal standard

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967), *In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). In rejecting a claim under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that: (i) the prior art suggests the claimed invention; and (ii) the prior art indicates that the invention would have a reasonable likelihood of success. *In re Dow Chemical Company,* 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988).

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication. The teaching

or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on the applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680 16 USPQ2d 1430 (Fed. Cir. 1990)

Further, a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984).

ii. Rejection of Claims 1-2 and 6-9 under 35 U.S.C. § 103(a) over WO 94/23740 in view of Dinbergs

WO 94/23740

WO 94/23740 discloses a method for stimulating bone formation in an animal by administering to the animal an effective amount of a hydrophilic polymer-conjugated growth factor in solution. The reference does not teach coupling growth factors to a polymeric scaffold. WO 94/23740 describes a method for covalently coupling various growth factors such as TGF-β or TGF-β_2 to a polymer such as polyethylene glycol using a linking compound such as n-hydroxysuccinimide (see page 11, lines 13-28). WO 94/23740 discloses that polymer-conjugated growth factors can stimulate bone formation at lower dosage levels as compared to the unmodified growth factor, and at higher dosage levels, the polymer-conjugated growth factors promote a net increase in bone formation as compared to the unmodified growth factor

which causes a net decrease in bone mass (see abstract). WO 94/23740 does not mention using TGF-β to increase extracellular matrix production. Furthermore, the reference notes significant increases in proliferation of osteoblast-like cells, which was interpreted as bone stimulation (see page 20, lines 7-22).

In summary, WO 94/23740 simply teaches that a polymer-growth factor conjugate promotes bone formation, part of which is attributed to an increase in proliferation of osteoblast-like cells, better than the unmodified growth factor. This reference differs from the claimed invention in several respects:

(1) WO 94/23740 does not teach coupling a matrix-enhancing molecule to a tissue engineering *scaffold* in an effective density to increase extracellular matrix production *without increasing cellular proliferation* (claim 1).

(2) Specifically referring to TGF-β, WO 94/23740 does not teach an effective density of between 1 and 100 ng TGF-β/mL (claim 1).

(3) WO 94/23740 makes no mention of attaching cells to a polymeric scaffold (claim 2).

(4) WO 94/23740 does not teach coupling matrix-enhancing molecules to tethers which are covalently bound to the scaffold (claim 6).

(5) WO 94/23740 does not teach a tissue engineering scaffold that is a hydrogel (claim 7), wherein the hydrogel may be alginate, collagen, hyaluronic acid, and polyethylene glycol polymers (claim 8).

(6) WO 94/23740 does not teach coupling TGF-b to the hydrogel in a concentration of 1 to 100 ng TGF-b/mL (claim 9).

Dinbergs

Dinbergs addresses the assumption that cells optimally respond to controlled release of growth factors (see page 29822, col. 2, first full paragraph), by comparing changes in cellular proliferation between sustained release and bolus administration of soluble bFGF and TGF-β1 (see abstract). These studies are carried out using alginate/heparin-Sepharose microspheres containing the relevant growth factors (see page 29823, col. 1, last paragraph). The growth factors are not coupled to a polymeric scaffold, but instead are encapsulated by a polymeric matrix and released as soluble growth factors.

Dinbergs comes to the conclusion that, in the case of TGF-β1, sustained release is a far less optimal means of administering the growth factor than bolus injection (see page 29827, col. 1, first full paragraph). This statement alone is sufficient to demonstrate that Dinbergs teaches away from the claimed invention. This conclusion is supported by data shown in Figures 3A and 3B, which Dinbergs summarizes with the statement that a bolus of TGF-β1 inhibits vascular cells up to 3.8-fold more efficiently than the same amount of TGF-β1 if control-released (see page 29822, col. 2, last paragraph, bridging page 29823). Dinbergs does not discuss nor suggest that extracellular matrix production may be enhanced without increasing cellular proliferation. While Dinbergs makes mention that TGF-β mediates accumulation of extracellular matrix (page 29822, col. 2, last paragraph), and later shows that sustained-release TGF-β is a poor inhibitor of cellular proliferation (Figures 3A and 3B), this in no way suggests that matrix accumulation may be stimulated independently of cellular proliferation.

Furthermore, the Examiner states that Dinbergs teaches coupling TGF-β to a polymeric scaffold in a 1-10 ng/mL concentration (see page 4, Final Office Action). However, the text referred to by the Examiner is directed to growth factor concentrations use in investigation of the rate of controlled release of soluble growth factors from the extracellular matrix (see page 29823, col. 2, last full paragraph, bridging page 29824). Looking at the text relevant to production of microspheres containing TGF-β (see page 29823, *EVAc Microsphere Preparation and Growth Factor Incorporation*), Dinbergs states that the end concentration is "3 ng of TGF-β1/microsphere." Assuming the volume of the *micro*spheres is far less than 1mL, it is clear that the concentration does not fall within the 1-10ng/mL concentration as alleged by the Examiner, nor in the 1-100ng/mL concentration as claimed by Appellants.

In summary, Dinbergs states that sustained-release of soluble TGF-β1 is not as effective as bolus administration. Dinbergs differs from the claimed invention in several aspects:

(1) Dinbergs does not disclose coupling a matrix-enhancing molecule to a tissue engineering *scaffold* in an effective density to *increase extracellular matrix production* without increasing cellular proliferation (claim 1).

(2) Specifically referring to TGF-β, WO 94/23740 does not disclose an effective density of between 1 and 100 ng TGF-β/mL (claim 1).

(3) Dinbergs makes no mention of attaching cells to a polymeric scaffold (claim 2).

(4) Dinbergs does not disclose coupling matrix-enhancing molecules to tethers which are covalently bound to the scaffold (claim 6).

(5) Dinbergs does not disclose a tissue engineering scaffold that is a hydrogel (claim 7), wherein the hydrogel may be alginate, collagen, hyaluronic acid, and polyethylene glycol polymers (claim 8).

(6) Dinbergs does not disclose coupling TGF-b to the hydrogel in a concentration of 1 to 100 ng TGF-b/mL (claim 9).

The combination of WO 94/23740 with Dinbergs

The combination does not make obvious claim 1

With regard to claim 1, neither reference discloses coupling matrix-enhancing molecules to a tissue engineering *scaffold*. WO 94/23740 discloses the use of soluble polymer-growth factor conjugates. Dinbergs teaches encapsulated growth factors which are released as soluble growth factors. Furthermore, neither reference discloses coupling TGF-β in an effective density to enhance extracellular matrix production without increasing cell proliferation.

The combination does not make obvious claim 2

Neither reference discloses the additional limitation of attaching cells to the scaffold.

The combination does not make obvious claims 3 and 5

Neither reference discloses the coupling of matrix-enhancing molecules such as angiotensin II and ascorbic acid to a polymeric scaffold.

The combination does not make obvious claim 4

Neither reference discloses the coupling of matrix-enhancing molecules such as insulin-like growth factors to a polymeric scaffold.

The combination does not make obvious claim 6

Neither reference discloses coupling matrix-enhancing molecules to tethers which are coupled to the scaffold.

The combination does not make obvious claims 7-9

Neither reference makes any mention of a polymeric scaffold, much less a polymeric scaffold that is a hydrogel.

The Examiner has provided no reasons for his rejections of the dependent claims over WO 94/23740 in view of Dinbergs. The references clearly do not make mention of any of the additional limitations. Accordingly, the combination of WO 94/23740 with Dinbergs does not make obvious the claimed elements.

iii. Rejection of Claims 1-2 and 6-9 under 35 U.S.C. § 103(a) over WO 96/27657 in view of Dinbergs

WO 96/27657

WO 96/27657 discloses cell growth substrates with tethered cell growth effector molecules. The publication teaches a method for making a tissue engineering scaffold comprising coupling of various growth factors and extracellular matrix molecules to a polymeric matrix via flexible tethers for purposes of ***stimulating proliferation of cells*** (see abstract and claims 1, 13 and 31). WO 96/27657 teaches that localized growth factors result in a higher rate of cell growth and are effective at lower dosages as compared to soluble growth factor (see page 5, line 27). The reference does not teach coupling matrix-enhancing molecules to a polymeric scaffold to increase extracellular matrix production. Specifically in the case of TGF-β, WO

96/27657 does not disclose an effective density of 1 to 100 ng TGF-β/mL. The reference also fails to disclose a tissue engineering scaffold that is a hydrogel. The Examiner incorrectly argues that WO 96/27657 discloses a method of enhancing production of extracellular matrix molecules such as collagen (see page 6 of Final Office Action). The cited text (page 17, lines 1-4) is directed to materials for construction of tissue regeneration devices, listing collagen as a candidate since it is a natural polymer.

The combination of WO 96/27657 and Dinbergs

There is no suggestion in either reference to incorporate the teachings of the other. The claims of WO 96/27657 are directed to methods and compositions for stimulating eukaryotic cell growth. Dinbergs teaches TGF-β as an inhibitor of cellular proliferation, not a promoter of proliferation. WO 96/27657 describes the use of immobilized TGF-β, while Dinbergs discloses soluble TGF-β, administered as a bolus or sustain-released from microspheres. Furthermore, Dinbergs clearly concludes that soluble, bolus administration of TGF-β is the preferred method of administration. Therefore, not only do the references not suggest their combination, the combination is destructive to the teachings of Dinbergs.

Even if the teachings of the references are combined, the combination does not suggest the claimed methods.

The combination does not make obvious claim 1

Neither WO 96/27657 nor Dinbergs disclose the benefits of enhancing extracellular matrix formation without increasing cellular proliferation. Nor do the references disclose

coupling TGF-β to a polymeric scaffold in an effective density (1-100 ng/mL) to enhance cellular proliferation.

The combination does not make obvious claims 3 and 5

Neither reference discloses the coupling of matrix-enhancing molecules such as angiotensin II and ascorbic acid to a polymeric scaffold.

The combination does not make obvious claims 7-9

Neither reference teaches the additional limitations of claims 7-9, relating to a hydrogel scaffold.

(c) Unexpected Results

i. Sufficient Proof of Unexpected Results

An example of evidence which proved that the claimed method produced unexpected results is described in *In re Orfeo*, 440 F.3d 439 (C.C.P.A. 1971). In *Orfeo*, the court held that the applicant demonstrated that the claimed azeotropic mixture demonstrated unexpected results and was therefore patentable. This particular mixture used less power during a refrigeration process than was predicted based on the prior art. Appellants used Pennington's law to calculate the power requirements for the claimed azeotrope to a number of mixtures of CHF_3 and $CClF_3$. In each case, the azeotrope had a higher power requirement. However, when the actual power requirement was tested, the azeotrope had a lower power requirement (1.59 HP/ton) than would have been predicted using Pennington's law (1.72 HP/ton). Further, the power requirement for a refrigerant typically increases as a higher pressure refrigerant is employed. However, the claimed azeotrope had a higher pressure than either of its components, but had a lower power

requirement than the components (see *Id.* At 440). The court held that this was sufficient proof of unexpected results (*Id.*).

ii. The claimed methods have unexpected results in view of the prior art.

Appellants' combination of immobilized growth factor technology and the inhibitory properties of TGF-β results in an unexpectedly improved method of enhancing extracellular matrix formation without an increase in cell proliferation. The cited prior art, as discussed above, shows or describes increases in cellular proliferation when TGF-β is introduced to the cell population. WO 94/23740 notes significant increases in proliferation of osteoblast-like cells (see page 20, lines 7-22); WO 96/27657 is directed to methods and compositions for stimulating eukaryotic cell growth (see abstract and claims 1, 13 and 31); and Dinbergs argues that TGF-β1 should not be released in a sustained manner because of it's inability of reduced efficacy in inhibiting cell growth, citing an 18.0-fold increase in endothelial cell number over the original plating density and a 115.0-fold increase for smooth muscle cells (see page 29825, col.1, last paragraph, bridging col. 2).

In many tissue engineering applications it is important to avoid undesirable enhancement of cell growth. For example, in vascular tissue engineering, over-proliferation of the smooth muscle cells can lead to a failure of the tissue engineering construct due to lumenal narrowing. Appellants have devised a method for increasing extracellular matrix production without increasing cellular proliferation, by coupling matrix-enhancing molecules to a polymeric scaffold in an effective density. This is unexpected in light of the prior art: WO 94/23740 discloses a soluble polymer-conjugated growth factor which increases cellular proliferation; WO 96/26757

discloses growth factors coupled to scaffolds which increase cellular proliferation; and Dinbergs teaches TGF-β sustain-released from microspheres is unable to effectively inhibit cell proliferation.

Appellants present data (see Tables 5 and 6) illustrating an increase in extracellular matrix formation without a corresponding increase in cellular proliferation. This result is unexpected in view of the prior art and therefore not obvious to one with ordinary skill in the art.

(9) SUMMARY AND CONCLUSION

For the foregoing reasons, Appellants submits that claims 1-9 are not obvious over the prior art.

Respectfully submitted,

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Date: February 3, 2004

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U.S.S.N. 09/935,168
Filed: August 21, 2001
APPEAL BRIEF

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Peggy Bailey
Peggy Bailey

Date: February 3, 2004

Appendix: Claims On Appeal

1. A method for making a tissue engineering scaffold for inducing formation of extracellular matrix by cells bound to the scaffold comprising coupling matrix-enhancing molecules to the scaffold in an effective density to elicit production of extracellular matrix without increasing cellular proliferation, wherein when the matrix-enhancing molecules are TGF-β, the TGF-β is coupled to the matrix by a polymer tether having a molecular weight between 2000 and 6000 and is in a density between 1 and 100 ng TGF-β/ml or in a concentration of between about 4×10^{-6} and 4×10^{-3} nmol/mL.

2. The method of claim 1 further comprising attaching cells to the scaffold.

3. The method of claim 1 wherein the matrix-enhancing molecules are angiotensin II.

4. The method of claim 1 wherein the matrix-enhancing molecules are insulin-like growth factor.

5. The method of claim 1 wherein the matrix-enhancing molecules are ascorbic acid.

6. The method of claim 1 wherein the matrix-enhancing molecules are covalently coupled to tethers which are covalently coupled to the scaffold.

7. The method of claim 1 wherein the scaffold is a hydrogel.

8. The method of claim 7 wherein the hydrogel is formed of a polymer selected from the group consisting of alginate, collagen, hyaluronic acid, and polyethylene glycol polymers.

9. The method of claim 7 wherein the matrix-enhancing molecules are TGF-β coupled to the hydrogel in a concentration of between about 4×10^{-6} and 4×10^{-3} nmol/mL.

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